A Case of Inflammatory Nonscarring Alopecia Associated With the Tyrosine Kinase Inhibitor Nilotinib

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Importance: Nilotinib, a recently approved multitargeted tyrosine kinase inhibitor targeting the BCR-Abl translocation involved in chronic myelogenous leukemia, reportedly produces alopecia according to the package insert, but clinical and histologic descriptions of the alopecia are lacking.

Observations: A 33-year-old woman with chronic myelogenous leukemia developed widespread alopecia involving scalp and body hair within weeks after starting nilotinib therapy. Biopsies revealed perifollicular lymphocytic inflammation and evidence of follicular injury but normal hair density, consistent with a nonscarring alopecia.

Conclusions and Relevance: Nilotinib therapy may induce perifollicular inflammation and widespread persistent alopecia. We present the first clinical and histologic description of this potential adverse effect. Further investigation into the underlying mechanism of this adverse effect may produce insights into the hair growth cycle as well as potential therapeutic targets.


TYROSINE KINASE INHIBITORS (TKIs) are a class of anticancer drugs that target abnormal signaling pathways involved in cell growth and proliferation. An association between tyrosine kinase inhibitors (TKIs) and alopecia has been recognized for both epidermal growth factor receptor (EGFR)-specific and multitargeted TKIs. While the alopecia associated with EGFR TKIs has been well documented, the clinical and histologic features of alopecia associated with multitargeted TKIs are not well described. Reported cutaneous adverse effects of multitargeted TKIs include subungual splinter hemorrhages, acral erythema, xerosis, facial erythema, periocular edema, hair and skin dyspigmentation, perifollicular papulopustular skin eruption, and varied patterns of alopecia. Nilotinib, a recently approved multitargeted TKI targeting the BCR-Abl translocation involved in chronic myelogenous leukemia, reportedly produces alopecia according to the package insert, but clinical and histologic descriptions of the alopecia are lacking. This case report represents the first description, to our knowledge, of alopecia associated with nilotinib treatment, including clinical and histologic features.

REPORT OF A CASE

A 33-year-old woman receiving routine prenatal care was diagnosed as having chronic myelogenous leukemia. A month after delivering a healthy child, she was started on nilotinib therapy (Tasigna; Novartis Pharmaceuticals), 300 mg twice daily. Within a few weeks of starting treatment, she developed diffuse alopecia affecting her scalp, eyebrows, and body hair. Physical examination of the scalp revealed perifollicular erythema and hyperkeratosis but no evidence of scarring (Figure 1). Eyelashes and nails were spared, and the patient denied any associated symptoms. Abdominal skin showed flesh-colored to slightly erythematous follicular papules (Figure 2). Two punch biopsies were performed, on the right scalp and abdomen, and submitted for horizontal sectioning (Figure 3).

Review of the scalp biopsy specimen revealed a normal follicular density, with a total of 44 hair follicles, consistent with a nonscarring alopecia. The terminal to vellus hair ratio was approximately 3:1, and the anagen to telogen ratio was 47%: 53% (Figure 3A). Despite a normal hair density, there was evidence of follicular injury that included perifollicular fibrosis, polytrichia, and loss of sebaceous glands (Figure 3B and C). There was lymphocytic inflammation of mild to moderate intensity that was perivascular and perifollicular. There was also spongiosis and some dyskeratosis of the infundibular outer root sheath. The epidermis appeared normal.

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The abdominal skin biopsy revealed a solitary vellus hair follicle with mild perifollicular lymphocytic inflammation. The patient’s clinical picture remained unchanged as the patient continued with nilotinib treatment over the ensuing 8 months.

**COMMENT**

In nilotinib phase 1 trials, alopecia was reported in 6% of patients, although specific description of the alopecia was not presented. To our knowledge, this case report is the first clinical and histologic description of nilotinib-induced alopecia. Nilotinib was approved in 2007 for treatment of Philadelphia chromosome–positive chronic myelogenous leukemia. It is a multitargeted tyrosine kinase inhibitor that preferentially inhibits the BCR-Abl tyrosine kinase but has also been shown to interact with discoidin domain receptors, platelet-derived growth factor receptor (PDGFR), and c-kit receptor.

The temporal relationship between widespread alopecia affecting the scalp, eyebrows, and body and the initiation of nilotinib therapy (within weeks) favor nilotinib as the primary etiologic factor in this alopecia. The
scalp biopsy result confirmed telogen effluvium, with a telogen count of 53%. This could be related to post partum telogen effluvium, related to her illness, or due to nilotinib use. However, the histologic findings that are not compatible with telogen effluvium include the loss of sebaceous glands, perifollicular fibrosis, polytrichia, and lymphocytic inflammation, also suggestive of an inflammatory process that may produce some permanent scarring. Sunitinib, sorafenib, and dasatinib, multitarget TKIs with similar targets to nilotinib, have been reported to cause a follicular-based eruption and alopecia.4,9 One of these skin manifestations is an eruptive hyperkeratotic folliculitis and papulopustular eruption, which is described as morphologically similar to the skin eruption from EGFR inhibitors, though less frequent and less severe.10 Sorafenib and sunitinib produce 1 or more cutaneous adverse effects in 74% and 81% of patients, respectively.11 The described perifollicular skin eruption seems similar to that seen in our patient, although with more pronounced erythema. Clinical trials for sorafenib and sunitinib report alopecia in 18% and 6% of patients, respectively.10,12 Sorafenib-induced alopecia is described as thinning and/or patchy hair loss on the scalp, slowed beard growth in men, and occasionally involving other hair-bearing areas. It appears between weeks 3 and 15 of treatment. Regrowth was noted even with continued treatment in some cases.5

The literature on alopecia caused by multitargeted tyrosine kinase inhibitors is lacking, but the similar binding sites (PDGFR and c-Kit) between nilotinib, sorafenib, and sunitinib suggest a potential single mechanism responsible for the alopecia. Sorafenib and sunitinib have the highest affinity for vascular endothelial growth factor receptor, PDGFR, c-Kit, and Fms-like tyrosine kinase 3,10,13 whereas nilotinib targets discoidin domain receptors, BCR-Abl, PDGFR, and c-Kit, in order of decreasing affinity.8 Although pharmacokinetic studies do not indicate EGFR binding with these TKIs, authors have suggested a possibility of interaction between PDGF and EGFR in vivo.8,11,13

Another possible explanation is the role of PDGF within the hair follicle. As previously mentioned, nilotinib has been shown to interact with PDGF as well as BCR-Abl. Neither BCR-Abl nor nilotinib has been linked to hair loss in the literature. Platelet-derived growth factor (PDGF), however, has been shown to affect induction and maintenance of the anagen phase in murine models.10 Mice injected with PDGF exhibited maintenance of the anagen phase, while mice injected with anti-PDGF antibodies showed transition of anagen hairs into catagen phase. Thus, PDGF inhibition significantly alters the hair follicle cycle toward shedding. The observation of an increased anagen to telogen ratio in this murine model is also consistent with the pattern seen in our patient, although a recent pregnancy and resultant telogen effluvium may also account for this finding.

This case is the first detailed description of nilotinib-induced alopecia, as well as the first description of the underlying histologic features seen with multitargeted TKI-induced alopecia. The perifollicular skin eruption is similar although more diffuse than descriptions with other TKIs, which seem to be limited to the central face and upper trunk.10 Historically, the increased number of catagen and telogen hairs corresponds with the effects seen in EGFR inhibitor–induced alopecia and with the PDGFR-inhibited murine model.1,2,10,17 Further investigation into the underlying mechanism of this adverse effect may produce insights into the hair growth cycle as well as potential therapeutic targets.

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